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Phytosomes, an Emerging Platform for Herbal Based Drug Delivery

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Abstract: Recently, medicinal plants have been chosen as a therapeutic aid for multifactorial diseases. The standardization challenges, solubility, bioavailability, absorption, and permeation hinder its clinical application. The phospholipid-compatible molecular complexes of the phytosome/herbosome are developed using plant extract/phytoconstituent along with a phospholipid. Phytosomes may improve the hydrophilicity/lipophilicity of the encapsulated compound. Phytosome formulation may be administered with low doses and an enhanced duration of action compared to plant extracts or conventional dosage forms. The interactions of the loaded plant extract/phytoconstituent and phospholipids with a hydrogen bond enable the development of phospholipid complexes in the phytosomes.In this vesicular type of system, the encapsulated plant extract/compound will be present at the core of the formulation, whereas the targeting moieties will be present at the surface of the vesicular system. This novel drug delivery system is occupied with bioactive phytoconstituents, surrounded by a hydrophilic nature and with other lipophilic layers to enhance absorption and bioavailability. This review contains an overview of Phytochemicals, phytosomes, and their preparation and characterization techniques, along with recent phytosome development for nasal, topical, parenteral, and oral delivery with a particular concern on the phytosomes commercially available in the market and phytosomes under clinical trials.

Keywords: phytosome; lipid; permeation; vesicle; phytoconstituent.

1. Introduction

Phytochemicals are naturally occurring, bioactive polyphenolic substances that are frequently found in plants. These phytochemicals and phytoconstituents may have therapeutic and dietary advantages. Phytoconstituents can be bioactive, have low cytotoxicity, and help create a variety of phyto-based formulations [1- 4]. The antioxidant capacity of the phytoconstituent, which scavenges free radicals, is one of its potential qualities. Due to their adaptable qualities, some phytoconstituent categories may function as nutraceuticals.

The cutting-edge lipid-based delivery method, i.e., the innovative vesicular nano-based drug delivery technology known as phytosomes, may increase the bioavailability and

absorption of medications. In phytosomal formulation, phospholipids and plant extracts or phytoconstituents produce lipid-compatible molecular complexes. Poorly water-soluble phytoconstituent's solubility may be improved here in the phytosomes. Phospholipids are typically used in the formulation of phytosomes. The absorption, bioavailability, pharmacokinetic, and pharmacodynamic properties are improved by phytosome formulation. Phytosomes improve the stability of the formulation, increase encapsulation effectiveness, and control the formulation's release kinetics. In the case of phytosomal formulation, an envelope-like coating was seen to enclose the active loaded phytoconstituent. Phytosomes also provide protection against the deterioration caused by digestive enzymes; even for polar phytoconstituents, phytosomes' increased rate of absorption results in a lower quantity of active ingredients needed to exert a biological impact. The charged phospholipid head is created when the polar groups in the phytoconstituent engage with the phospholipid's hydrogen bonds. The bioavailability of phytosomes is higher than that of liposomes and niosomes. Flavonoids, alkaloids, polyphenols, terpenoids, and other phytoconstituents are better encapsulated by phytosomes. Phytosomes improve the absorption of polar, lipid-insoluble phytoconstituents. The dose of the phytosome formulation may be lowered due to the enhanced absorption. The phytoconstituents and carriers have a chemical connection that makes the phytosome more stable in nature. The plasma concentration of the loaded phytoconstituents increases with the absorption of phytosomes in the gastrointestinal tract. Because phospholipids are present, a hydrogen connection can form between the polar head and the active phytoconstituent. Figure 1 is a schematic illustration of phytosomes.

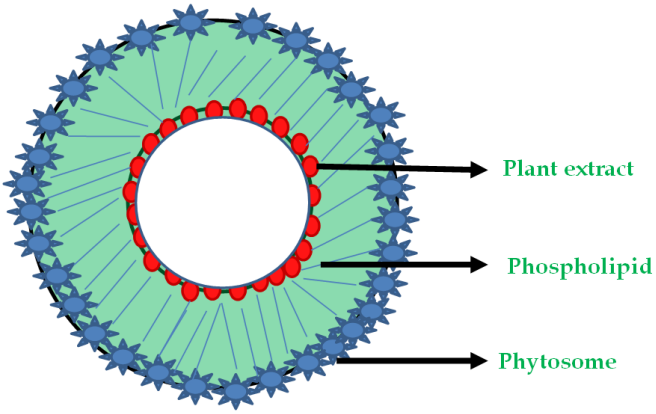

Figure 1. Schematic representation of phytosome.

The term "phytochemicals" refers to various naturally occurring bioactive substances plants produce. Different interaction rates may occur between the living organisms and these phytochemicals, including phenolics, alkaloids, carbohydrates, lipids, terpenoids, and other nitrogen-containing molecules. Phytochemicals, often known as plant chemicals, are a diverse group of naturally occurring bioactive substances plants create. The term "bioactive" describes how these substances can interact with various parts of living things to exhibit their advantageous effects. The key categories of phytochemicals with the most structural variation are phenols, alkaloids, carbohydrates, lipids, terpenoids, and other nitrogen-containing molecules. Additionally, there are a number of phytochemical subgroups depending on variations in the biogenesis or biosynthesis route. Figure 2 displays the various phytoconstituents derived from plants.

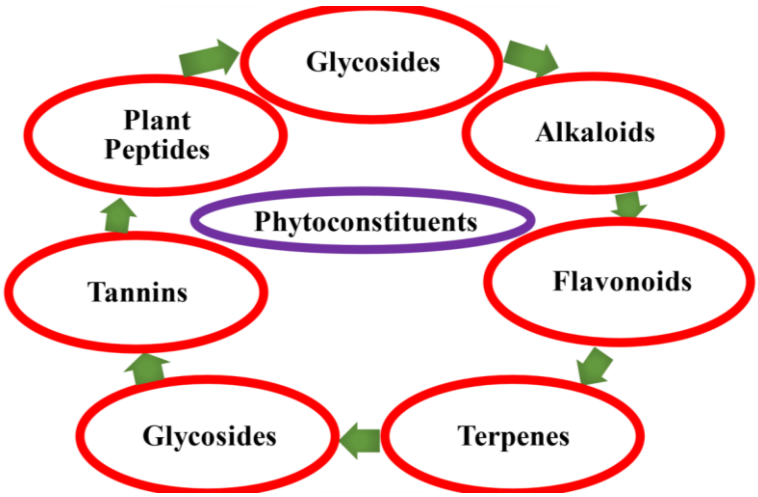

Figure 2. Schematic representation of plant-based phytoconstituents.

The phytoconstituents with active hydrogen atoms, such as -COOH, -OH, -NH_2, etc., may be integrated with the phytosome structure. The formulation of phytosomes results from the interaction of phospholipids like phosphatidylcholine with the appropriate phytoconstituent/herbal extract. The phospholipid head group keeps the phytosome stable.

Phytosomes share a functional moiety with liposomes and transferosomes. Under an aqueous environment, they remain stable between 4°C and 25°C for up to three months. When applied topically, phytosomes, based on their excipients, cause skin penetration. During the formation of the phytosome, the H-bond connection between the phospholipid and the encapsulated phytoconstituents was maintained. Long fatty acid chains are unnecessary for the complex formation when phytosomes develop; instead, they exchange the polar heads. In the case of phytosomes, the lipophilic lipid moiety is used for formulation development, and the hydrophilic moiety (head) binds to the loaded phytoconstituents (polar). The delivery of different phytoconstituents is efficient and affordable to phytosomal technology. Phytosomes differ from other phyto-based carrier systems due to their enhanced capability to protect the intrinsic stability of the loaded phytoconstituents.

Reduced particle size, better solubility, and improved absorption are the defining characteristics of phytosomes [5-8]. The process by which phytosomes are made favors a chemical interaction between phospholipids in the form of hydrogen bonds between the polar side front of the phospholipids and the polar functional group of the secondary metabolites, which results in the formation of a particular pattern in addition to the phytoconstituent.

Phytosomes serve a significant role in the formulation development of numerous medicines, nutraceuticals, and cosmeceuticals. The few companies focused on developing phytosomes are Indena, Jamieson Natural Resources, Thorne Research, Natural Factors, and Nature Herb. Phytosomes are passive, non-intrusive, and marketed and commercialized in a ready-to-use state. Due to the capacity of the loaded phytoconstituent, which may increase the loaded phytoconstituent's absorption rate, phytosome-based formulations only require a small dose. Figure 3 depicts the evolution of phytosome formulations.

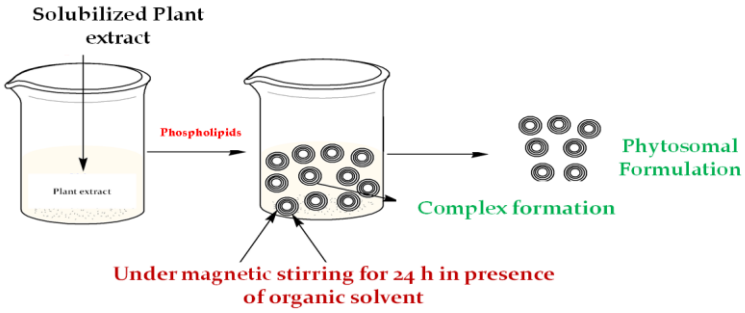

Figure 3. The development process of phytosomes.

2. Characterization of Phytosomes

Using FT-IR Spectrophotometric analysis, the phytosomes can be identified by their compatibility nature. In this case, the signature of the loaded extract/phytoconstituent, the excipients, and the formulated phytosomes were compared for their significant compatibility behavior characteristics. Zeta sizers can measure both the charge, or zeta potential value, and the particle size of the produced phytosome, which is significant. The polydispersity index (PDI) values of the generated phytosomes can be used to determine the uniformity and aggregation potential of the phytosomes. The PDI index can measure the aggregation, uniformity, and effectiveness of the generated phytosomes. Transmission and scanning electron microscopies can be used to examine the phytosomes' surface morphology. Utilizing a thermogravimetric analyzer, one may examine the thermal stability of phytosomes and record their thermal behavior in response to temperature changes for later research [8]. High-performance thin Layer Chromatography (HPTLC) and an appropriate, optimized mobile phase may determine the amount of phytoconstituents loaded or encapsulated within the phytosomes. The HPTLC works on the principle of separation and quantification of phytoconstituents, and the amount of phytoconstituent present in the sample will be checked based on the Rf value. The Rf value will then be calculated and compared to the standard phytoconstituent's. High-Performance Liquid Chromatography (HPLC) will sometimes be used when measuring the loaded phytoconstituent in the phytosomes. The dialysis bag method or centrifugal method may be used to examine the *In vitro* release properties of phytosomes; in this case, the samples will be examined using HPTLC/HPLC. According to the recommendations [9, 10], the HPLC/HPTLC method for the quantification/release studies should be confirmed. According to ICH standards, the accelerated stability of phytosomes should also be taken into consideration when analyzing their long- and short-term stability [11, 12]. When applied topically, the generated phytosomes' ability to penetrate the skin can be tested using models of excised skin. Animal (rat/rabbit) skin may be utilized to achieve this objective and further analyzed using HPTLC/HPLC. The *In vitro* characterization studies of phytosomes are shown in Figure 4.

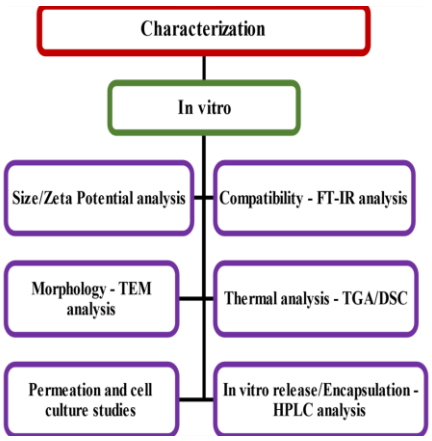

Figure 4. *In vitro* characterization studies of phytosomes.

3. Phytosomes Formulation Approaches

Phytoconstituents are typically integrated with the phospholipid complex during the solvent evaporation method to prepare phytosomes, which requires the reaction temperature to be optimized to achieve the maximum phytoconstituent entrapment. The lipids in an organic solvent are brought into contact with the medication treated with the aqueous phase in mechanical dispersion type. Under low pressure, the collected organic solvents will evaporate. The phytoconstituent was extracted and then treated with an appropriate organic solvent to create a complex of phospholipids and phytoconstituents when using the salting-out method. Plant extract or phytoconstituent that has been dissolved in phospholipid and maintained magnetic stirring is used in the lyophilization process to create phytosomes. When using the anti-solvent approach, the phytoconstituent or plant extract that has been dissolved in a specific solvent is treated with the anti-solvent, and the resulting precipitate is obtained. In the Rotary vacuum evaporation approach, phospholipid and plant extract are treated with a solvent in the rotary vacuum evaporator, and the solvent is then evaporated to produce the phytosomes [13]. Figure 5 displays the benefits of phytosomes for drug administration. The chemical bonding of phytosomes ensures the stability of phytosomes; this may also be supported by the stoichiometric molar ratio of phospholipids utilized in the formulation of phytosomes.

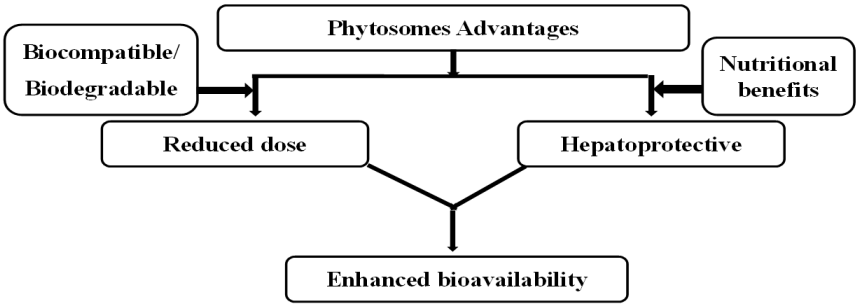

Figure 5. Drug delivery advantages of phytosomes.

4. Phospholipids

Phospholipids (complex lipids) in most cell membranes are amphiphilic molecules that hold hydrophobic fatty acid chains in addition to hydrophilic moieties. PH has a significant impact on the ability of polar moieties to associate. When phospholipids are exposed to water, they become hydrated and form lamellar or hexagonal phases. The phospholipids are also used as an emulsifier. Because phospholipids include unsaturated fatty acids, they are more quickly

oxidized. The phosphate group, hydrophilic residue, and amino-alcohol sphingosine/glycerol backbone make up the phospholipids. Phospholipids include phosphatidyl choline and phosphatidyl serine. Phospholipids form the lipid bilayer. When phospholipids are exposed to a lipid-based environment, micelles are formed; during this process, the phospholipid head and tail self-assemble [14–16]. The distinctive property of phytosomes was their ability to aggregate.

5. Phytosomes for Ocular Drug Delivery

The ocular drug delivery techniques use phytosomes. The use of prodrugs is increased because the presence of esterase causes N-acetyl carnosine to be hydrolyzed. Here, L-carnosine and lipoid 75 were treated with methanol and Milli Q water and refluxed for one hour at 40°C to produce a phospholipid complex [17]. They found that L-carnosine phytosomes had 2.4 to 5.6 times quicker penetration than L-carnosine solution. The phytosome technology helps phospholipids to enter the posterior portion of the eye with more selectivity and specificity. Furthermore, phytosomes enhance the effectiveness of the specific phytoconstituent loaded when used for ocular drug delivery. The phospholipid LECIVA-S70 to make Hesperetinnaturosomes using solvent evaporation has been reported. They evaluated the developed lipid-based system's compatibility, thermal behavior, shape, and diffraction pattern. They discovered that compared to pure hesperetin, natural hesperetin is 10 times more soluble in water [17].

In comparison to pure hesperetin (23%) and the Hesperetinphysical combination (28%), the corneal penetration of Hesperetinnaturosomes dramatically increases (>53%). This suggests that phytosomes are more effective in accelerating corneal permeation [18–20]. Figure 6 illustrates the advantages of phytosomes for ocular drug delivery. The challenges associated with the delivery of phytosomes through the ocular route involve poor corneal permeability, which may limit the entry of drugs loaded in the phytosomes. The presence of anatomical and physiological barriers also limits the entry of drugs into the eye, which may lead to poor absorption and very low ocular bioavailability. The lacrimal secretions may also lead to poor retention time and decreased permeability across the corneal epithelium. Conjunctival blood circulation also affects topical drug absorption. Overall, these may significantly lose the administered drugs through topical administration.

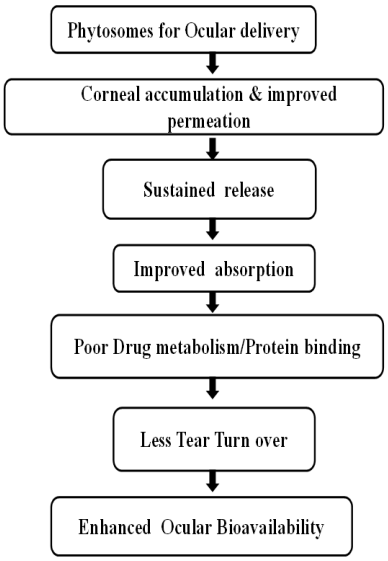

Figure 6. Ocular drug delivery of phytosomes.

6. Phytosomes for Nasal Drug Delivery

The nasal route, which involves olfactory or trigeminal nerves exiting the brain at the respiratory epithelium or olfactory neuroepithelium and entering the nasal cavity, is a dependable way to cross the blood-brain barrier. This creates quick, non-invasive access into the cerebrospinal fluid as well as interaction with the mucosal tissue. For the transfer of anti-Alzheimer's drugs into the brain, lipidic nanoparticles, emulsions, vesicles, gels, liposomes, etc., have demonstrated promising results. This increases the permeability and related bioavailability. The formulation method, size, zeta potential, and therapeutic action of the encapsulated drug influence the effective targeted administration via the nasal route. The standard intranasal transport system combines passive partitioning, carrier-mediated transport, and the paracellular pathway in order to target the brain [21–23].

Our team reported the phytosomes containing "Geophilarepensmethanolic leaf extract" using soy phosphatidylcholine. In order to provide a better penetration effect at the nasal cavity for the enhanced treatment of Alzheimer's disease, we further transformed the phytosomes into intranasal gel using hydroxypropyl methylcellulose as a gelling agent and incorporating transcutol P. We found that the mature phytosomes have a spherical form, measure 444.93 ±25.24 nm in size, and contain 51.88± 1.025% of the methanolic leaf extract of Geophila repens. At 60 minutes, it was discovered that the *In vitro* release was 45.84± 5.6%. The Geophila repens methanolic leaf extract-based phytosome intra-nasal gel demonstrated improved nasal permeability in comparison to the Geophila repens methanolic leaf extract, as well as better acetylcholinesterase inhibition (97.87± 6.84%) as compared to MEGR (69.86± 5.68%), which was shown to be higher and with substantial [24]. The nasal drug delivery benefits of phytosomes are shown in Figure 7.

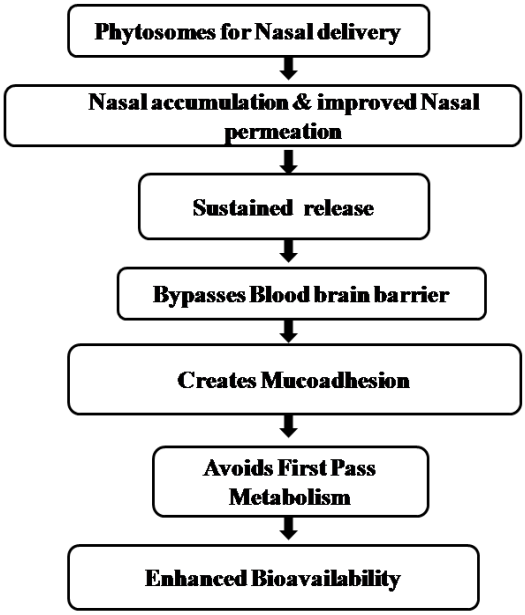

Figure 7. Nasal drug delivery of phytosomes.

7. Phytosomes for Topical Delivery

The topical drug delivery techniques use phytosomes. *Ocimum Basilicum* topical phytosomal gel was created using lecithin, cholesterol, and Carbopol 934. The *Ocimum Basilicum* extract was used to create the phytosomes, and they were evaluated for their

morphology, yield, stability, and ability to prevent microbial growth [25]. The produced phytosomes demonstrated improved cutaneous permeability. Stearic acid, cetyl alcohol, liquid paraffin, triethanolamine, glycerin, and other ingredients have all been mentioned in topical soy phytosome cream reports [26]. This cream has been found to be naturally non-irritating. Hesperetin-loaded phospholipid-based nano vesicular systems were developed using a solvent evaporation process that included a phospholipid complex. They noted that the new formulation improved the therapeutic efficacy, solubility, and penetration (>53%) of the encapsulated Hesperetin [27]. The phospholipid present in the phytosomes interfaces with the loaded phytoconstituent through the generation of an H-bond between the polar head of the phospholipid and the polar capabilities of the phytoconstituent. They significantly improve the skin penetration of the loaded phytoconstituents. Phytosomes enhance the permeation of loaded phytoconstituents due to their peculiar nanosize characteristics, quickly being delivered or transported across the cell membrane and into the bloodstream.

8. Phytosomes for Parenteral Delivery

The mitomycin C-loaded soybean phosphatidylcholine complex-based phytosomes employing solvent evaporation in conjunction with nanoprecipitation has been reported. They noticed that the mature phytosomes have a small size of 210.87 nm, a PDI of 0.251, and a charge of 33.38 mV. The spherical phytosomes had a biphasic release pattern, first releasing in a burst and then continuing to release over time. The produced phytosomes showed a notable lethal effect in H22 cells, a superior, dose-dependent curative inhibitory effect on tumor growth [28].

9. Phytosomes for Oral Drug Delivery

Jain S et al. developed cefixime-loaded phytosomes for oral drug administration in 2019 by utilizing phospholipid S100 in various millimolar ratios under vacuum drying and reflection [29]. The formulation was found to be in the nano-sized range with a prolonged release pattern. Quercetin phytosomes using food-grade lecithin have been reported to increase the solubility of quercetin. They saw improvements in both *In vitro* solubility and oral absorption while avoiding adverse effects [30]. The solubility of quercetin phytosomes is unaffected by the highly acidic conditions that prevail in the gastrointestinal situation. Here, an enterocyte membrane was seen to release the hydrophilic quercetin into the lipid environment, supporting quercetin's penetration into the bloodstream.

10. Phytosomes Available in the Market

Under the brand name Casperome, Boswellia extract-loaded phytosomes were sold by Indena for the treat acute diarrhea. These phytosomes have the potential to normalize intestinal motility, promote the production of loose and watery stools, and shorten the duration of motility imbalance. Ginkgo biloba leaves were used to create another nutraceutical called GinkgoselectPhytosome, which has antioxidant action, cognitive support, brain function, and vascular health. The hepatoprotective effect of GinkgoselectPhytosome may be connected to its antioxidant and free radical scavenging activity of the loaded extract, according to Naik et al.'s 2008 study on Rifampicin-induced hepatotoxic rats [31]. Swanson is the brand name used to advertise Hawthorn Phytosome, an herbal supplement for cardiovascular health. Available in liquids and capsules, this phytosome contains 3% vitexin. The commercially available sun

care products, after-sun products, soothing and lenitive products, available in the form of emulsions, masks, gels, and creams made from Terminalia sericea extract and incorporating phospholipids are all made with sericoside phytosome. Sericoside phytosome has an anti-wrinkle effect. The sericoside from Terminalia sericea was isolated and extracted for use in the creation of the Sericoside phytosome. Sericoside phytosome has been used to treat skin conditions in Africa and Asia. The Meriva phospholipid-based curcumin phytosome has a sustained release pattern, antioxidant potential, and higher absorption than curcumin extracts with optimized cytokine production. In a 2010 study, GianniBelcaro et al. reported Meriva's long-term efficacy and safety, a curcumin-phosphatidylcholine phytosome that reduces joint pain and enhances joint function. They noticed that "Mervia" could be employed for osteoarthritis control over the long term [32].

Catechin, epicatechin, epigallocatechin, and epigallocatechin-3-gallate are the main components of green tea. The primary total green tea polyphenols, which may be helpful in treating breast cancer, are epigallocatechin-3-gallate. By creating a phytosome utilizing lecithin and a caffeine-free green tea catechin extract, epigallocatechin-3-gallate tissue distribution has been reported. They were created as granules (sachets) and might be ready to dissolve in water. The phytosome was given daily for 4 weeks at a dose of 300 mg, which is equivalent to 44.9 mg of epigallocatechin-3-gallate, to 12 patients with early-stage breast cancer for the trial. Measurement of epigallocatechin-3-gallate levels in plasma, urine, breast cancer tissue, and adjacent healthy breast tissue after (total) enzymatic hydrolysis and before (free) enzymatic hydrolysis. All tumor tissue samples contained epigallocatechin-3-gallate at levels that could be detected. This may have been accomplished as a result of the phytosomes' improved absorption when taken orally [33].

The milk thistle (Silybum marianum) is a plant with the main component flavonolignan silybin, which plays a significant role in hepatoprotective action and is used in hepatoprotective therapy in clinical settings. The silybin has been created as a phytosome in granule form using soy lecithin, which can float in water. This formulation was given to patients with early breast cancer, and the distribution of silybin in the breast tissue was studied. In biological samples (plasma, urine, breast cancer, and surrounding normal tissue), silybin levels measured by LC-MS/MS before and after enzymatic hydrolysis show higher levels of silybin in blood along with accumulation in breast tumor tissue without significantly altering blood levels of IGF-I, nitric oxide, or Ki-67 after oral administration [34].

By controlling three types of genes, including transporters, phase II detoxifying enzymes, and endogenous antioxidants, The transcription factor nuclear factor erythroid 2-related factor 2, which regulates the cellular defense mechanism, has been controlled. The best phytosome was selected by the development of luteolin-loaded phytosomes employing a variety of phospholipids, including phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserin. The cotreatment of luteolin phytosome with doxorubicin with decreased Nrf2 gene expression and improved mRNA level in the cells resulted in the highest percentage of cell death in the instance of MDA-MB 231 cells. The expression of the Nrf2 gene likewise decreases dramatically downstream of the Ho1 and MDR1 genes. Utilizing phytosomal technology increases luteolin's solubility and its therapeutic effectiveness. With increased pharmacokinetic and pharmacological performance, this is a suitable option for cardiovascular, anti-inflammatory, immunomodulator, and anticancer therapy [35].

By evaluating 2D and 3-dimensional cell-culture models, the antitumor efficacy of curcumin phytosomes for breast cancer treatment has been reported. The tumor growth was

also suppressed with histological evidence of vascular rupture, RBC extravasation, necrosis, tumor stroma, and inflammation. The expression of cyclin D also decreased. When curcumin and 5-fluorouracil were treated together, lipid peroxidation was reduced, and MDA/SOD levels were elevated [36,37]. Curcumin phytosomes in a xenograft mouse model (female BALB/c) were used to demonstrate the biological activity of fluorouracil in suppressing tumor growth. The modulation of MDA levels, catalase, total thiol concentration, and SOD in breast cancer tissue has produced this result.

Monascus yellow pigments Monascin and ankaflavin, as well as a phytosomal formulation based on resveratrol folate-conjugated casein micelles for active targeting, were developed from fungal sources. Compared to the free drugs, the phytosomal formulation demonstrated monomodal-based nanosize distribution, sustained release properties, strong hemocompatibility, and improved cytotoxicity in MCF-7 breast cancer cells. For the effective treatment of breast cancer, this would be preferable [38].

Silibinin, a naturally present polyphenolic flavonoid, was isolated from milk thistle (Silybum marianium). Silymarin was made from milk thistle crude extract. The commercially available Silibinin phytosome has been administered orally to 13 prostate cancer patients throughout 91 dose courses spaced out over four weeks; they noticed hyperbilirubinemia, grade 1-2 bilirubin elevations in 9 of the 13 patients, grade 3 toxicity, and one patient who had elevated alanine aminotransferase levels, but no grade 4 toxicity. Silibinin phytosomes were well tolerated in patients receiving the indicated phase II dose in cases of advanced prostate cancer with asymptomatic hepatotoxicity [39].

In a trial, it has been examined the blood levels of silybin after administering 13 g of silybin phytosome daily over 14 to 31 days in the case of prostate cancer patients. One patient experienced a grade 4 post-operative thromboembolic event, four cases of diarrhea, and asymptomatic grade 2 hyperbilirubinemia. The initial silybin concentration was found to be 19.7 M, with an average of 1.2 M observed in blood plasma. At the harvested prostate tissue, 496.6 pmol/g of silybin was observed without any significant changes in the levels of IGF-I and IGFBP-3 with grade 4 post-operative thromboembolic event was observed in one patient, 4diarrhoeacases and asymptomatic grade 2 hyperbilirubinemia observed in one patient [40]. Low quantities of silibinin are seen in prostate tissue despite transiently greater blood silybin phytosome concentrations. The short half-life of silibinin, the brief course of therapy in this trial, or an active process eliminating silibinin from the prostate may all contribute to its lack of tissue penetration. Even though many phytosome-based formulations are available in the market, the market analysis of the phytosomes depends on the type of phospholipid and the price utilized for the development of phytosomes.

11. Phytosomes and Permeation Enhancing Property

To provide a more potent therapeutic effect, the drug molecules must travel through the intracellular, intercellular, and trans follicular routes in order to enter the systemic circulation. Diffusion is the main procedure if the drug enters the cell through the intracellular pathway. The issue is that the hydrophilic domains of the intracellular pathway are difficult for highly lipophilic drugs to pass through. Hydrophilic drug molecules must travel through the layers. By salting out domperidone using phosphatidylcholine and piperine (a P-glycoprotein inhibitor). The phytosomes with a significantly higher oral bioavailability of domperidone (79.5%) than the pure drug have been reported [42]. Due to their diverse properties, phytosomes are effective in enhancing the penetration of drugs. Due to the permeation of

sinigrin and the presence of glucosinolate, the Sinigrin phytosome has the ability to heal wounds. Free sinigrin has a permeation property of 0.0730 g/ml, according to their ex vivo skin permeation upon the skin, but sinigrin converted into a phytosome complex demonstrated a permeability of 0.5155 g/ml [43]. The permeation parameters of the alkaloid-loaded phytosome from *Tinospora cordifolia* were 1.85 times greater than those of the pure fraction when it was produced using 30% soy lecithin and cholesterol. Alkaloid-loaded phytosomes derived from Tinospora cordifolia demonstrate a higher potential for alkaloid incorporation permeability improvement [44]. The highly lipophilic chemical curcumin-loaded phytosomes have been reported. They also tested the curcumin phytosomes' ex-vivo penetration into the rat colon and found that it was enhanced 4 times compared to curcumin suspension [45]. The lipid phosphatidylcholine was used to create rutin phytosomes, and they found a superior ex vivo permeation effect in excised Rat abdomen skin. Rutin's lipophilic nature makes it difficult for it to penetrate. They observed that phosphatidylcholine significantly contributed to the rutin's passage through the hydrophilic viable dermis and the lipophilic stratum corneum to the epidermal-dermal site [46]. Without causing skin irritation, the *Geophila repens* (L.) phytosomes infused into nasal gel demonstrated substantial *In vitro* nasal mucosa permeability. The various permeation enhancers reported for the development of phytosomes include transistor P, oleic acid, poloxamer 188, poloxamer 407, etc. The permeation process and its route are shown in Figures 8 and 9, respectively.

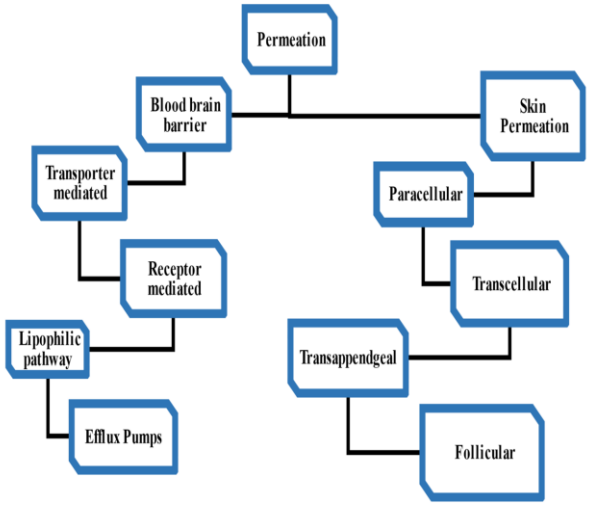

Figure 8. Permeation process of phytosomes.

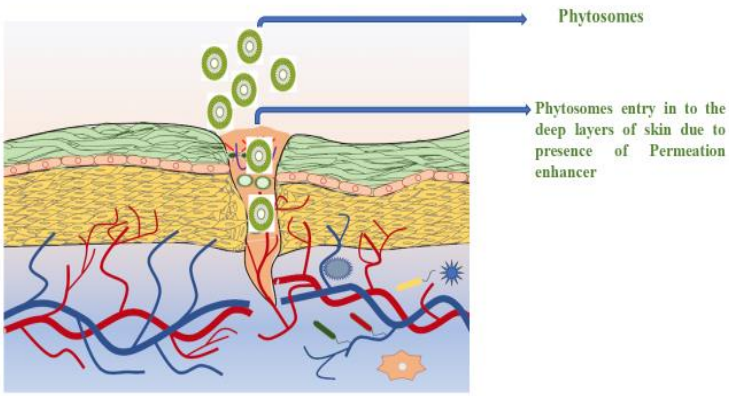

Figure 9. Permeation route of phytosomes.

12. Stimuli-Responsive and Targeted Phytosomes

The most efficient way to enhance a formulation's therapeutic response is to build the system as stimuli-responsive. Internal (pH, redox potential, or enzymes) and external (heat, magnetic field, or light) stimuli trigger an encapsulated drug's release. These stimuli lead to membrane testability, which allows the medication to be freed from its encapsulation. The recent emphasis on creating stimuli-responsive phytosomal compositions has become more apparent in the current environment. The effect of site-specific targeting can be obtained by attaching a targeting ligand, such as the RGD peptide or transferrin, to targeted phytosomes. Using a poly-L-lysine coat and hyaluronic acid, which showed a negative charge, it was revealed that ursolic acid-loaded nanophytoliposomes had dual stimuli-sensitive properties. The stimuli-responsive behaviors contributed to the more substantial tumor-inhibitory effect that was seen. The selenium-deposited tri phytosomes using the melting-hydration/in situ reduction approach has been reported, and they found that the selenium-deposited tri phytosomes released selenium more slowly than free phytosomes in both 0.1 M HCl and pH 6.8 phosphate buffer saline [47]. The phytosomes that are more than 40 kDa due to enhanced permeation and retention effect and a nano-metric size range of 100-1200 nm target the tumor cells by passive targeting approach, which may enhance the therapeutic effect of the encapsulated drug at the site. This method is the most effective for tumor therapy. Different phyto-based formulations such as niosomes, exosomes, liposomes, including phytosomes, etc., for the encapsulation of rutin, genistein, quercetin, etc., have been reported recently for various ailments such as cancer, rheumatoid arthritis, diabetes mellitus including COVID-19 [48-62]. The superiority of stimuli-based phytosomal/targeted phytosomes compared to conventional phytosomal formulations is that these formulations may offer a site-specific action.

13. Phytosomes Effect at the Cell Culture Level

When compared to free Mitomycin C, the cytotoxic effect of mitomycin C-loaded phytosomes in H22 cells demonstrated superior cytotoxic activity in a dose-dependent manner. Mitomycin C-soybean phosphatidylcholine complex loaded in phytosomes showed increased cellular uptake in HeLa cells as well as higher accumulation in H22 tumor-bearing mice [63]. Codium tomentosum Phytosomes employing phosphatidylcholine have been reported, and they noted that the generated phytosomes displayed low particle size and polydispersity. Additionally, the complex had a greater octanol-water partition coefficient than the isolated fraction [64].

14. Clinical Trials

Various forms of phytosomes are under clinical studies at different stages under this regimen, with the search for phytosomes in NIH US National Library of Medicine, Clinical Trials. Gov 8 studies were found, among which Quercetin as Phytosome formulation (500 mg) is under clinical trial for treating chronic fatigue, sleep assessment, and muscle performance assessment. In community-based studies, Quercetin Phytosome is under phase III trial as an adjuvant for SARS-CoV-2 infection. For Patients with EGFR mutant lung adenocarcinoma, the combined treatment with Erlotinib (Tarceva) and Silybin phytosome (Siliphos) is under phase II trial. The combined effect of Bergamot phytosome and artichoke leaf dry extract combination product to reduce high cholesterol levels is under clinical trial. The grape seed extract-based phytosomes are potentially used for early-stage lung cancer treatment and are

under phase II of a clinical trial. In order to enhance the absorption of green tea, phytoformulation incorporating phospholipids along with piperine under the name GreenselectPhytosomeas, a booster of absorption for various phenolics, is under phase IV clinical trial. The anticancer efficacy of silibinin obtained from milk thistle has been documented. For prostate cancer, Silybin Phytosome, as an oral form, has shown beneficial effects in men with prostate cancer. The efficacy of early stages of lung cancer has been checked using Grape seed extract-based phytosome formulation, which is under clinical trial (ClinicalTrials.gov Identifier: NCT04515004, accessed date: 28 August 2021). This study concluded that the phytosomal formulation had delayed the planned surgery by>14 days. The different phytosomal formulations under clinical trials are shown in Table- 1.

Table 1. Phytosomes under clinical trials.

S No	Title	Outcome	Sponsor	Phase	Reference
1	Trial to Study the Adjuvant Benefits of Quercetin Phytosome in Patients With COVID-19	Boosts natural immunity	Liaquat University of Medical & Health Sciences	III	NCT04578158
2	A Phase II Study to Assess Efficacy of Combined Treatment with Erlotinib (Tarceva) and Silybin-phytosome (Siliphos) in Patients with EGFR Mutant Lung Adenocarcinoma	Blocks EGFR signal	MedicalLogic	II	NCT02146118
3	Artichoke and Bergamot Phytosome	Effective hypocholesterolemic agent	Azienda di Servizialla Persona di Pavia	NA	NCT04697121
4	LeucoselectPhytosome for Neoadjuvant Treatment of Early Stage Lung Cancer	Anticancer effect	VA Office of Research and Development	II	NCT04515004
5	Effects of GreenselectPhytosome® on Weight Maintenance After Weight Loss in Obese Women	-	IstitutoAuxologicoItaliano	IV	NCT02542449
6	The Effect of High-dose Silybin-phytosome in Men with Prostate Cancer	Anticancer effect	University of Colorado, Denver	II	NCT00487721
7	Grape seed extract Early stages lung cancer	Anticancer effect	-	II	NCT04515004,

15. Patents on Phytosomes Based Drug Delivery

The technology of monomer, dimer, or oligomeric forms of flavonoid-based complex compounds along with phospholipids to process their preparation and pharmaceutical and cosmetic compositions has been patented. They found that when flavonoids and phospholipids are combined, their lipophile character gets effectively absorbed upon oral/parenteral/topical administration and increases the therapeutic effectiveness of the flavonoids. The phospholipid complex of olive fruits/leaf extract has been patented (EP 1844785). The method of phytosomal quercetin preparation with a particle size of 2–12 nm has been developed using soybean seeds utilizing a chloroform-ethanol mixture (1:1)under an ultrasound frequency of 22 kHz (RU2680809C2). Phytosomes of ginkgo biloba, milk thistle, grape seed, hawthorn, green tea, and ginseng have been reported. Recently, at the research level, a few phytosomes have been reported, such as Carvacrol Phytosomes for enhanced wound healing, Ginger Rhizomes and Rosehips loaded Phytosomes, hydroalcoholic extract of Adiantum capillus-veneris loaded phytosomes for microbial infections.

16. Conclusion

This advanced form of phytoconstituent/plant extract-loaded drug delivery system is better absorbed with improved permeation at the oral, topical, nasal, and parenteral routes. Since the development approaches of phytosomes are elementary and reproducible, attempts to standardize the phytosomal formulation with proper validation are crucial at this stage. Improving solubility, permeability, stability, long-term dosing, chemical and physical degradation resistance, and pharmacological efficiency are among the merits of phytosome formulations over typical herbal formulations. These phytosomal formulations may still be conceptualized with the involvement of stimuli-responsive characteristics or by targeted-based approaches.

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Conflict of Interest

The authors do not declare any conflict of interest.

References

1. Barani, M.; Sangiovanni, E.; Angarano, M.; Rajizadeh, M.A.; Mehrabani, M.; Piazza, S.; Gangadharappa, H.V.; Pardakhty, A.; Mehrbani, M.; Dell'Agli, M.; Nematollahi, M.H. Phytosomes as Innovative Delivery Systems for Phytochemicals: A Comprehensive Review of Literature. *Int. J. Nanomed*. **2021**, *16*, 6983-7022, https://doi.org/10.2147/IJN.S318416.
2. Susilawati, Y.; Chaerunisa, A.Y.; Purwaningsih, H. Phytosome drug delivery system for natural cosmeceutical compounds: Whitening agent and skin antioxidant agent. *J. Adv. Pharm. Technol. Res*. **2021**, *12*, 327-334, https://doi.org/10.4103%2Fjaptr.JAPTR_100_20.
3. Khanzode, M.B.; Kajale, A.D.; Channawar, M.A.; Gawande, S.R. Review on phytosomes: A novel drug delivery system. *GSC Biol. Pharm. Sci*. **2020**, *13*, 203–211, https://doi.org/10.30574/gscbps.2020.13.1.0345.
4. Alharbi, W.S.; Almughem, F.A.; Almehmady, A.M.; Jarallah, S.J.; Alsharif, W.K.; Alzahrani, N.M.; Alshehri, A.A. Phytosomes as an Emerging Nanotechnology Platform for the Topical Delivery of Bioactive Phytochemicals. *Pharmaceutics* **2021**, *13*, 1475, https://doi.org/10.3390/pharmaceutics13091475.
5. Priya, B.; Singh, S.K.; Kumar, D.; Visht, S. Phytosome: A Novel Drug Delivery System for Herbal Drugs. *The Global Journal of Pharmaceutical Research*. **2013**, *2*, 1452-1458.
6. Limongi, T.; Susa, F.; Marini, M.; Allione, M.; Torre, B.; Pisano, R.; di Fabrizio, E. Lipid-Based Nanovesicular Drug Delivery Systems. *Nanomaterials* **2021**, *11*, 3391, https://doi.org/10.3390/nano11123391.
7. Hashemzadeh, H.; Hanafi-Bojd, M.Y.; Iranshahy, M.; Zarban, A.; Raissi, H. The combination of polyphenols and phospholipids as an efficient platform for delivery of natural products. *Sci. Rep.* **2023**, *13*, 2501, https://doi.org/10.1038/s41598-023-29237-0.
8. Nandhini, S.; Ilango, K. Development and characterization of a nano-drug delivery system containing vasaka phospholipid complex to improve bioavailability using quality by design approach. *Res. Pharm. Sci*. **2020**, *16*, 103-117, https://doi.org/10.4103/1735-5362.305193.

9. Sharma, S.; Sahu, A.N. Development, Characterization, and Evaluation of Hepatoprotective Effect of Abutilon indicum and Piper longum Phytosomes. *Pharmacognosy Res*. **2016**, *8*, 29-36, https://doi.org/10.4103/0974-8490.171102.
10. Freag, M.S.; Saleh, W.M.; Abdallah, O.Y. Laminated chitosan-based composite sponges for transmucosal delivery of novel protamine-decorated tripterine phytosomes: Ex-vivo mucopenetration and in-vivo pharmacokinetic assessments. *Carbohydr. Polym*. **2018**, *188*, 108–120, https://doi.org/10.1016/j.carbpol.2018.01.095.
11. Tan, Q.; Liu, S.; Chen, X.; Wu, M.; Wang, H.; Yin, H.; He, D.; Xiong, H.; Zhang, J. Design and evaluation of a novel evodiamine- phospholipid complex for improved oral bioavailability. *AAPS PharmSciTech*. **2012**, *13*, 534–547, https://doi.org/10.1208/s12249-012-9772-9.
12. Yue, P.-F.; Zhang ,W.-J.; Yuan, H.-L.; Yang, M.; Zhu, W.-F.; Cai, P.-L.; Xiao, X.-H. Process optimization, characterization and pharmacokinetic evaluation in rats of ursodeoxycholic acid-phospholipid complex. *AAPS PharmSciTech*. **2008**, *9*, 322–329, https://doi.org/10.1208/s12249-008-9040-1.
13. Gaurav, V.; Paliwal, S.; Singh, A.; Pandey, S.; Siddhiqui, M.A. Phytosomes: Preparation, Evaluation and Application. *Int. J. Res. Eng. Sci.* **2021**, *9*, 35-39.
14. Dai, Y.; Tang, H.; Pang, S. The Crucial Roles of Phospholipids in Aging and Lifespan Regulation. *Front. Physiol*. **2021**, *12*, 775648, https://doi.org/10.3389/fphys.2021.775648.
15. Lu, M.; Qiu, Q.; Luo, X.; Liu, X.; Sun, J.; Wang, C.; Lin, X.; Deng, Y.; Song, Y. Phyto-phospholipid complexes (phytosomes): A novel strategy to improve the bioavailability of active constituents. *Asian J. Pharm. Sci*. **2019**, *14*, 265-274, https://doi.org/10.1016/j.ajps.2018.05.011.
16. Suriyakala, P.C.; Babu, S.N.; Rajan, S.D.; Prabakaran, L. Phospholipids as versatile polymer in drug delivery systems. *Int. J. Pharm. Pharm. Sci*. **2014**, *6*, 8-11.
17. Abdelkader, H.; Longman, M.R.; Alany, R.G.; Pierscionek, B. Phytosome-hyaluronic acid systems for ocular delivery of L-carnosine. *Int. J. Nanomed*. **2016**, *14*, 2815-2827, https://doi.org/10.2147/ijn.s104774.
18. Gurav, S.; Usapkar, P.; Gurav, N.; Nadaf, S.; Ayyanar, M.; Verekar, R.; Bhole, R.; Venkataramaiah, C.; Jena, G.; Chikhale, R. Preparation, characterization, and evaluation (in-vitro, ex-vivo, and in-vivo) of naturosomal nanocarriers for enhanced delivery and therapeutic efficacy of hesperetin. *PLoS ONE* **2022**, *17*, e0274916, https://doi.org/10.1371/journal.pone.0274916.
19. Ogita, R.; Shital, S.; Aishwarya, P.; Manojkumar, N.; Shrinivas, M. Phytosomes–A Novel Approach in Herbal Drug Delivery System. *Asian J. Res. Pharm. Sci*. **2018**, *8*, 151-154.
20. Udapurkar, P.P.; Bhusnure, O.G.; Kamble, S.R. Diosmin Phytosomes: Development, Optimization and Physicochemical Characterization. *Indian J. Pharm. Educ. Res*. **2018**, *52*, S29–S36.
21. Rayate, Y.; Shewale, S.; Patil, A.; Nitalikar, M.; Mohite, S. Phytosomes–A Novel Approach in Herbal Drug Delivery System. *Asian J. Res. Pharm. Sci*. **2018**, *8*, 151-154, https://doi.org/10.5958/2231-5659.2018.00027.9.
22. Semalty, A.; Semalty, M.; Rawat, M.S.M.; Franceschi, F. Supramolecular phospholipids–polyphenolics interactions: The PHYTOSOME® strategy to improve the bioavailability of phytochemicals. *Fitoterapia* **2010**, *81*, 306–314, https://doi.org/10.1016/j.fitote.2009.11.001.
23. Gandhi, A.; Dutta, A.; Pal, A.; Bakshi, P. Recent Trends of Phytosomes for Delivering Herbal Extract with Improved Bioavailability. *J. Pharmacogn. Phytochem*. **2012**, *1*, 6–14.
24. Rajamma, S.S.; Krishnaswami, V.; Pradu, S.L.; Kandasamy, R. *Geophila repens* phytosome-loaded intranasal gel with improved nasal permeation for the effective treatment of Alzheimer's disease. *J. Drug Deliv. Sci. Techol*. **2022**, *69*, 103087, https://doi.org/10.1016/j.jddst.2021.103087.
25. Raj, M.P.; Reichal, C.R.; Manju, S.; Shobana, M.; Sangeetha, M. Formulation and Characterization of Phythosomal Topical Gel of Ocimum Basilicum. *Res. J. Pharm. Techol*. **2022**, *15*, 4649-4654, https://doi.org/10.52711/0974-360X.2022.00780.
26. Aniket; Kumari, A.; Kumari, P.; Saurabh, S.; Khurana, L.; Rathore, K.S. Formulation and evaluation of topical soy-phytosome cream. *Ind. J. Pharm. Pharmacol*. **2015**, *2*, 105-112.
27. Suprit, D.S.; Nilesh, R.R.; Pradip, W.D.; Sushant, O.D.; Nilambari, S.G.; Shailendra, S.G.; Nishikant, A.R. Phospholipid Based Colloidal Nanocarriers for Enhanced Solubility and Therapeutic Efficacy of Withanolides. *J Drug Del Sci Tech*. 2022, 70, 103251.
28. Hou, Z.; Li, Y.; Huang, Y.; Zhou, C.; Lin, J.; Wang, Y.; Cui, F.; Zhou, S.; Jia, M.; Ye, S.; Zhang, Q. Phytosomes Loaded with Mitomycin C–Soybean Phosphatidylcholine Complex Developed for Drug Delivery. *Mol. Pharm.* **2013**, *10*, 90–101, https://doi.org/10.1021/mp300489p.

29. Jain, S.; Ancheriya, R.; Srivastva, S.; Soni, S.L.; Sharma, M. Formulation and Characterization of Cefixime Phytosomes for Oral Drug Delivery. *Asian J. Pharm. Res. Dev.* **1970**, *7*, 65-73, https://doi.org/10.22270/ajprd.v7i5.559.
30. Riva, A.; Ronchi, M.; Petrangolini, G.; Bosisio, S.; Allegrini, P. Improved Oral Absorption of Quercetin from Quercetin Phytosome®, a New Delivery System Based on Food Grade Lecithin. *Eur. J. Drug Metab. Pharmacokinet.* **2019**, *44*, 169-177, https://doi.org/10.1007/s13318-018-0517-3.
31. Naik, S.R.; Panda, V.S. Hepatoprotective effect of Ginkgoselect Phytosome in rifampicin induced liver injury in rats: evidence of antioxidant activity. *Fitoterapia* **2008**, *79*, 439-445, https://doi.org/10.1016/j.fitote.2008.02.013.
32. Belcaro, G.; Cesarone, M.R.; Dugall, M.; Pellegrini, L.; Ledda, A.; Grossi, M.G.; Togni, S.; Appendino, G. Efficacy and safety of Meriva®, a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients. *Altern. Med. Rev.* **2010**, *15*, 337-344.
33. Lazzeroni, M.; Guerrieri-Gonzaga, A.; Gandini, S.; Johansson, H.; Serrano, D.; Cazzaniga, M.; Aristarco, V.; Macis, D.; Mora, S.; Caldarella, P.; Pagani, G.; Pruneri, G.; Riva, A.; Petrangolini, G.; Morazzoni, P.; DeCensi, A.; Bonanni, B. A Presurgical Study of Lecithin Formulation of Green Tea Extract in Women with Early Breast Cancer. *Cancer Prev. Res.* **2017**, *10*, 363-370, https://doi.org/10.1158/1940-6207.capr-16-0298.
34. Lazzeroni, M.; Guerrieri-Gonzaga, A.; Gandini, S.; Johansson, H.; Serrano, D.; Cazzaniga, M.; Aristarco, V.; Puccio, A.; Mora, S.; Caldarella, P.; Pagani, G.; Pruneri, G.; Riva, A.; Petrangolini, G.; Morazzoni, P.; DeCensi, A.; Bonanni, B. A Presurgical Study of Oral Silybin-Phosphatidylcholine in Patients with Early Breast Cancer. *Cancer Prev. Res.* **2016**, *9*, 89–95, https://doi.org/10.1158/1940-6207.capr-15-0123.
35. Sabzichi, M.; Hamishehkar, H.; Ramezani, F.; Sharifi, S.; Tabasinezhad, M.; Pirouzpanah, M.; Ghanbari, P.; Samadi, N. Luteolin-loaded phytosomes sensitize human breast carcinoma MDA-MB 231 cells to doxorubicin by suppressing Nrf2 mediated signalling. *Asian Pac. J. Cancer Prev.* **2014**, *15*, 5311–5316, https://doi.org/10.7314/apjcp.2014.15.13.5311.
36. Hashemzehi, M.; Behnam-Rassouli, R.; Hassanian, S.M.; Moradi-Binabaj, M.; Moradi-Marjaneh, R.; Rahmani, F.; Fiuji, H.; Jamili, M.; Mirahmadi, M.; Boromand, N.; Piran, M.; Jafari, M.; Sahebkar, A.; Avan, A.; Khazaei, M. Phytosomal-curcumin antagonizes cell growth and migration, induced by thrombin through AMP-Kinase in breast cancer. *J. Cell Biochem.* **2018**, *119*, 5996-6007, https://doi.org/10.1002/jcb.26796.
37. Wu, P.; Gao, W.; Su, M.; Nice, E.C.; Zhang, W.; Lin, J.; Xie, N. Adaptive Mechanisms of Tumor Therapy Resistance Driven by Tumor Microenvironment. *Front. Cell Dev. Biol.* **2021**, *9*, 641469, https://doi.org/10.3389/fcell.2021.641469.
38. El-Far, S.W.; Helmy, M.W.; Khattab, S.N.; Bekhit, A.A.; Hussein, A.A.; Elzoghby, A.O. Folate conjugated vs PEGylated phytosomal casein nanocarriers for codelivery of fungal- and herbal-derived anticancer drugs. *Nanomedicine* **2018**, *13*, 1463–1480, https://doi.org/10.2217/nnm-2018-0006.
39. Flaig, T.W.; Gustafson, D.L.; Su, L.-J.; Zirrolli, J.A.; Crighton, F.; Harrison, G.S.; Pierson, A.S.; Agarwal, R.; Glodé, L.M. A phase I and pharmacokinetic study of silybin-phytosome in prostate cancer patients. *Invest. New Drugs* **2007**, *25*, 139–146, https://doi.org/10.1007/s10637-006-9019-2.
40. Flaig, T.W.; Glodé, M.; Gustafson, D.; van Bokhoven, A.; Tao, Y.; Wilson, S.; Su, L.-J.; Li, Y.; Harrison, G.; Agarwal, R.; Crawford, E.D.; Lucia, M.S.; Pollak, M. A study of high-dose oral silybin-phytosome followed by prostatectomy in patients with localized prostate cancer. *Prostate* **2010**, *70*, 848–855, https://doi.org/10.1002/pros.21118.
41. Huang, Z.; Brennan, C.S.; Zhao, H.; Liu, J.; Guan, W.; Mohan, M.S.; Stipkovits, L.; Zheng, H.; Kulasiri, D. Fabrication and assessment of milk phospholipid-complexed antioxidant phytosomes with vitamin C and E: A comparison with liposomes. *Food Chem.* **2020**, *324*, 126837, https://doi.org/10.1016/j.foodchem.2020.126837.
42. Islam, N.; Irfan, M.; Hussain, T.; Mushtaq, M.; Khan, I.U.; Yousaf, A.M.; Ghori, M.U.; Shahzad, Y. Piperine phytosomes for bioavailability enhancement of domperidone. *J. Liposome. Res.* **2022**, *32*, 172-180, https://doi.org/10.1080/08982104.2021.1918153.
43. Mazumder, A.; Dwivedi, A.; Fox, L.T.; Brümmer, A.; du Preez, J.L.; Gerber, M.; du Plessis, J. *In vitro* skin permeation of sinigrin from its phytosome complex. *J. Pharm. Pharmacol.* **2016**, *68*, 1577-1583, https://doi.org/10.1111/jphp.12594.
44. Thakur, A.L.; Patil, K.S. Formulation of Alkaloid Loaded Phytosomes fromTinospora cordifolia and ex-vivo Intestinal Permeability Study. *Indian J. Pharm. Educ. Res.* **2020**, *55*, 474- 482, https://doi.org/10.5530/ijper.55.2.85.

45. Allam, A.N.; Komeil, I.A.; Abdallah, O.Y. Tailor Made Phospholipid Based Curcumin Phytosomes: Fabrication, Characterization and Ex-Vivo Permeation. *IOSR J. Pharm. Biol. Sci.* **2016**, *11*, 120-127.
46. Das, M.K.; Kalita, B. Design and Evaluation of Phyto-Phospholipid Complexes(Phytosomes) of Rutin for Transdermal Application. *J. Appl. Pharm. Sci*. **2014**, *4*, 051-057, http://doi.org/10.7324/JAPS.2014.401010.
47. Chavda, V.P.; Vihol, D.; Mehta, B.; Shah, D.; Patel, M.; Vora, L.K.; Pereira-Silva, M.; Paiva-Santos, A.C. Phytochemical-loaded liposomes for anticancer therapy: an updated review. *Nanomedicine* **2022**, *17*, 547–568, https://doi.org/10.2217/nnm-2021-0463.
48. Anand, U.; Dey, A.; Chandel, A.K.S.; Sanyal, R.; Mishra, A.; Pandey, D.K.; De Falco, V.; Upadhyay, A.; Kandimalla, R.; Choudhary, A.; Dhanjal, J.K.; Dewanjee, S.; Vallamkondu, J.; Pérez de la Lastra, J.M. Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. *Genes Dis.* **2023**, *10*, 1367-1401, https://doi.org/10.1016%2Fj.gendis.2022.02.007.
49. Aqil, F.; Gupta, R.C. Exosomes in Cancer Therapy. *Cancers* **2022**, *14*, 500, https://doi.org/10.3390%2Fcancers14030500.
50. Alhakamy, N.A.; Fahmy, U.A.; Eldin, S.M.B.; Ahmed, O.A.A.; Aldawsari, H.M.; Okbazghi, S.Z.; Alfaleh, M.A.; Abdulaal, W.H.; Alamoudi, A.J.; Mady, F.M. Scorpion Venom-Functionalized Quercetin Phytosomes for Breast Cancer Management: *In vitro* Response Surface Optimization and Anticancer Activity against MCF-7 Cells. *Polymers* **2022**, *14*, 93, https://doi.org/10.3390/polym14010093.
51. Komeil, I.A.; Abdallah, O.Y.; El-Refaie, W.M. Surface modified genistein phytosome for breast cancer treatment: In-vitro appraisal, pharmacokinetics, and in-vivo antitumor efficacy. *Eur. J. Pharm. Sci.* **2022**, *179*, 106297, https://doi.org/10.1016/j.ejps.2022.106297.
52. Rondanelli, M.; Perna, S.; Gasparri, C.; Petrangolini, G.; Allegrini, P.; Cavioni, A.; Faliva, M.A.; Mansueto, F.; Patelli, Z.; Peroni, G.; Tartara, A.; Riva, A. Promising Effects of 3-Month Period of Quercetin Phytosome® Supplementation in the Prevention of Symptomatic COVID-19 Disease in Healthcare Workers: A Pilot Study. *Life* **2022**, *12*, 66, https://doi.org/10.3390/life12010066.
53. Sailaja, K.; Ahad, H.A.; Chinthaginjala, H.; Gudisipalli, R.; Rajyalakshmi, S.I.; Vagganagari, Y. Approaches to creating and past successful attempts on microspheres: A primer for aspiring researchers. *Res. J. Pharm. Dosage Forms Technol.* **2022**, *14*, 245-248, https://doi.org/10.52711/0975-4377.2022.00040.
54. Kumar, L.S.; Ahad, H.A. A Review on Progressive Trends in Pharmaceutical Nano Emulsions and their Assessment. *Res. J. Pharm. Technol.* **2022**, *15*, 3782-3789, https://doi.org/10.52711/0974-360X.2022.00635.
55. Fouziya, B.; Ahad, H.A.; Charan, D.S.; Vidya, J.S.; Reddy, U.C.; Reddy, P.N. Fabrication and Evaluation of Cefpodoxime Proxetil Niosomes. *Asian J. Pharm. Technol*. **2022**, *12*, 109-122, https://doi.org/10.52711/2231-5713.2022.00018.
56. Tachie, C.; Nwachukwu, I.D.; Aryee, A.N.A. Trends and innovations in the formulation of plant-based foods. *Food Prod. Process Nutr.* **2023**, *5*, 16, https://doi.org/10.1186/s43014-023-00129-0.
57. Abid, N.; Khan, A.M.; Shujait, S.; Chaudhary, K.; Ikram, M.; Imran, M.; Haider, J.; Khan, M.; Khan, Q.; Maqbool, M. Synthesis of nanomaterial's using various top-down and bottom-up approaches, influencing factors, advantages, and disadvantages: A review. *Adv. Colloid Interface Sci.* **2022**, *300*, 102597, https://doi.org/10.1016/j.cis.2021.102597.
58. Ratnadewi, D.; Widjaja, C.H.; Barlian, A.; Amsar, R.M.; Ana, I.D.; Hidajah, A.C.; Notobroto, H.B.; Wungu, T.D.K. Isolation of Native Plant-Derived Exosome-like Nanoparticles and Their Uptake by Human Cells. *Hayati. J. Biosci.* **2022**, *30*, 182–192, https://doi.org/10.4308/hjb.30.1.182-192.
59. Li, D.; Yao, X.; Yue, J.; Fang, Y.; Cao, G.; Midgley, A.C.; Nishinari, K.; Yang, Y. Advances in Bioactivity of MicroRNAs of Plant-Derived Exosome-Like Nanoparticles and Milk-Derived Extracellular Vesicles. *J. Agric. Food Chem.* **2022**, *70*, 6285–6299, https://doi.org/10.1021/acs.jafc.2c00631.
60. Zhang, Z.; Yu, Y.; Zhu, G.; Zeng, L.; Xu, S.; Cheng, H.; Ouyang, Z.; Chen, J.; Pathak, J.L.; Wu, L.; Yu, L. The Emerging Role of Plant-Derived Exosomes-Like Nanoparticles in Immune Regulation and Periodontitis Treatment. *Front. Immunol.* **2022**, *13*, 896745, https://doi.org/10.3389/fimmu.2022.896745.
61. Chen, N.; Sun, J.; Zhu, Z.; Cribbs, A.P.; Xiao, B. Edible plant-derived nanotherapeutics and nanocarriers: recent progress and future directions. *Expert. Opin. Drug Deliv.* **2022**, *19*, 409–419, https://doi.org/10.1080/17425247.2022.2053673.
62. Zhu, S.; Luo, C.; Feng, W.; Li, Y.; Zhu, M.; Sun, S.; Zhang, X. Selenium-deposited tripterine phytosomes ameliorate the antiarthritic efficacy of the phytomedicine via a synergistic sensitization. *Int. J. Pharm.* **2020**, *578*, 119104, https://doi.org/10.1016/j.ijpharm.2020.119104.

63. Li, Y.; Wu, H.; Jia, M.; Cui, F.; Lin, J.; Yang, X.; Wang, Y.; Dai, L.; Hou, Z. Therapeutic Effect of Folate-Targeted and PEGylated Phytosomes Loaded with a Mitomycin C–Soybean Phosphatidyhlcholine Complex. *Mol. Pharmaceutics* **2014**, *11*, 3017–3026, https://doi.org/10.1021/mp5001873.
64. Costa, M.; Soares, C.; Silva, A.; Grosso, C.; Delerue-Matos, C. Characterization of *Codium tomentosum* Phytosomes and Their Neuroprotective Potential. *Biol. Life Sci. Forum*. **2022**, *18*, 35, https://doi.org/10.3390/Foods2022-13009.